

## **REMARKS**

### ***STATUS OF THE CLAIMS***

Claims 1-91 are currently pending.

Claims 1, 2, 4-16, 20-27, 30-37, 40-45, 48-50, 54-57, 60, 61, 64-78, and 84-91 stand provisionally rejected under the doctrine of obviousness-type double patenting as unpatentable over claims 1-12, 18-20, and 24-32 of co-pending Application Ser. No. 10/119,118.

Claims 1-3, 6-12, 14-16, 27, 30-32, 36-38, 41-47, 49, 50, 64-66, 70-78, 84, and 85 stand rejected under 35 U.S.C. §102(a) as anticipated by Gao et al., WO 00/32189 ("Gao").

Claims 1, 2, 7-10, 14-16, 26, 27, 30-37, 41-45, 49, 50, 60, 61, 64-70, 73, 75-78, 84, and 85 stand rejected under §102(a) as anticipated by Tanida et al., U.S. Patent No. 6,214,378 ("Tanida I").

Claims 1, 2, 6-10, 14-16, 26, 27, 30-37, 41-45, 49, 50, 60, 61, 64-70, 73, 75-78, 84, and 85 stand rejected under §102(b) as anticipated by Tanida et al., WO 98/05310 ("Tanida II").

Claim 1, 2, 6, 14-16, 21-24, 26, 27, 30, 31, 35-37, 41, 49, 50, 54-57, 60, 61, 64, 65, 69-71, 75-78, and 84-91 stand rejected under §102(b) as anticipated by Black et al., U.S. Patent No. 5,733,909 ("Black").

Claims 4, 5, 17-19, 24, 25, 39, 42, 51-53, 58, 59, and 79-81 stand rejected under §103(a) as unpatentable over Gao in view of Hanna et al., U.S. Patent No. 4,601,894 ("Hanna").

Claims 13 and 48 stand rejected under §103(a) as unpatentable over Tanida II or Gao in view of Guess et al., U.S. Patent No. 6,054,455 ("Guess").

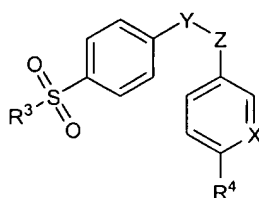
Claims 28, 29, 62, 63, 82, and 83 stand rejected under §103(a) as unpatentable over Tanida II.

Claim 74 stands rejected under §103(a) as unpatentable over Tanida II in view of Kawata et al., U.S. Patent No. 4,343,789 ("Kawata").

Claims 6, 7, 30, 41, 42, 64, and 71 have been cancelled.

Certain claims have been amended as described below without prejudice to filing one or more continuation or divisional applications.

Claim 1 has been amended to require that the selective cyclooxygenase-2 inhibitory drug has the formula



where X, Y, Z, R<sup>3</sup>, and R<sup>4</sup> are as defined in claim 1, and to require that the pharmaceutically acceptable solvent liquid is selected from the group consisting of glycols and glycol ethers. Claim 36 has been amended to require that the drug of low water solubility is a cyclooxygenase-2 inhibitory drug having the formula shown above for claim 1, and that the pharmaceutically acceptable solvent liquid is selected from the group consisting of glycols and glycol ethers. Claim 70 has been amended to require that the drug of low water solubility is a cyclooxygenase-2 inhibitory drug having the formula shown above for claim 1. Support for these amendments may be found, for example, in the specification at page 19, line 24 to page 21, line 6 and page 23, line 26 through page 25, line 15. Claims 7, 9, 20, 21 31-35, 42, 44, 54, 55, 65, 72, 84, and 85 have been amended to correct their dependencies. No new matter has been added by these amendments.

### **OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION**

Reconsideration is requested of the provisional rejection of claims 1, 2, 4-16, 20-27, 30-37, 40-45, 48-50, 54-57, 60, 61, 64-78, and 84-91 under the doctrine of obviousness-type double patenting as unpatentable over claims 1-12, 18-20, and 24-32 of co-pending Application Ser. No. 10/119,118.

Claims 6, 30, 41, 64, and 71 have been cancelled, rendering moot their provisional rejection under the doctrine of obviousness-type double patenting.

Pending allowance of the instant application, Applicant will submit a Terminal Disclaimer to obviate this rejection.

### ***REJECTIONS UNDER 35 U.S.C. §102***

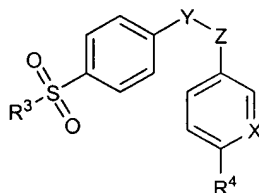
#### **Gao**

Reconsideration is respectfully requested of the rejection of claims 1-3, 6-12, 14-16, 27, 30-32, 36-38, 41-47, 49, 50, 64-66, 70-78, 84, and 85 under §102(a) as anticipated by Gao.

Claims 6, 7, 30, 41, 42, 64, and 71 have been cancelled, rendering moot their rejection as being anticipated by Gao.

#### **Claims 1-3, 8-12, 14-16, 27, 31, and 32**

Claim 1, as amended, is directed to an orally deliverable pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility having the formula



wherein X, Y, Z,  $R^3$ , and  $R^4$  are as defined in the claim; a pharmaceutically acceptable solvent liquid selected from the group consisting of glycols and glycol ethers; and a turbidity-decreasing polymer. Claim 1 recites that at least a substantial portion of the drug is in dissolved or solubilized form in the solvent liquid, and that the turbidity-decreasing polymer is present in an amount sufficient to substantially inhibit crystallization and/or precipitation of the drug in simulated gastric fluid.

Gao describes pharmaceutical compositions comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10

mg to about 1000 mg. These pharmaceutical compositions may also comprise one or more carrier materials or excipients selected from diluents, disintegrants, binding agents, wetting agents, and lubricants. See page 8, lines 1-3.

Nowhere does Gao describe a specific pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor of the formula shown above, a pharmaceutically acceptable glycol or glycol ether, and a turbidity decreasing polymer. On page 24, line 18 through page 30, line 7, Gao lists twenty embodiments of the compositions she describes. Each embodiment comprises celecoxib, croscarmellose sodium, polyvinylpyrrolidone, and either lactose or lactose monohydrate. Each also may optionally comprise sodium lauryl sulfate and/or magnesium stearate, or sodium lauryl sulfate, magnesium stearate, and/or microcrystalline cellulose. Importantly, none of these embodiments comprises a glycol or glycol ether recited by claim 1. Only two examples, Example 11-1 and 11-2 (formulation E), describe compositions comprising a glycol or a glycol ether. However, none of these compositions also comprise a turbidity decreasing polymer recited by claim 1. Thus, claim 1 is novel in view of Gao.

Claims 2, 3, 8-12, 14-16, 27, 31, and 32, which depend from claim 1, are also novel in view of Gao, for the same reasons given for claim 1, and for the additional features they add.

Claims 36-38, 43-47, 49, 50, 65, and 66

Contrary to the Office's suggestion, claim 36 is **not** directed to "an oral formulation comprising a COX-2 inhibitor of low water solubility, a solvent liquid, and a turbidity-decreasing polymer," page 3 of Office Action. Rather, claim 36, as amended, is directed to an orally deliverable pharmaceutical composition comprising a cyclooxygenase-2 inhibitory drug of low water solubility, a pharmaceutically acceptable solvent liquid selected from the group consisting of glycols and glycol ethers, and a cellulosic polymer. Claim 36 recites that at least a substantial portion of the drug is in dissolved or solubilized form in the solvent liquid, and that the cellulosic polymer is

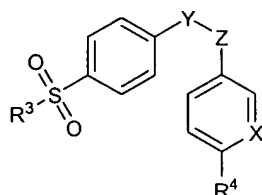
present in an amount sufficient to substantially inhibit crystallization and/or precipitation of the drug in simulated gastric fluid.

Nowhere does Gao describe a specific pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor, a pharmaceutically acceptable glycol or glycol ether, and a cellulosic polymer. None of the compositions described on page 24, line 18 through page 30, line 7 comprises a glycol or glycol ether recited in claim 36, and neither Example 11-1 nor Example 11-2 (formulation E) (which comprise celecoxib and polyethylene glycol (PEG)) describe compositions comprising a cellulosic polymer recited in claim 36. Thus, claim 36 is not anticipated by Gao.

Claims 37, 38, 43-47, 49, 50, 65, and 66, which depend from claim 36, are also novel in view of Gao, for the same reasons given for claim 36, and for the additional features they add.

#### Claims 70 and 72-78

Contrary to the Office's suggestion, claim 70 is **not** directed to "an oral formulation comprising a COX-2 inhibitor of low water solubility, a solvent liquid, and a turbidity-decreasing polymer," page 3 of Office Action. Rather, claim 70, as amended, is directed to an orally deliverable pharmaceutical composition comprising a cyclooxygenase-2 inhibitory drug of low water solubility in a high energy phase together with one or more pharmaceutically acceptable excipients, encapsulated within a capsule wall that comprises a turbidity-decreasing polymer in an amount effective to substantially inhibit crystallization and/or precipitation of the drug in simulated gastric fluid. The selective cyclooxygenase-2 inhibitory drug has the formula



wherein X, Y, Z, R<sup>3</sup>, and R<sup>4</sup> are as defined in claim 70. Although the composition of claim 70 may comprise a solvent liquid, claim 70 **does not require** a solvent liquid.

Nowhere does Gao describe a specific pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor having the structure shown above in a high energy phase **encapsulated within a capsule wall that comprises a turbidity-decreasing polymer**, as claim 70 requires, and thus claim 70 (and dependent claims 72-78) is novel in view of Gao.

**Claims 84 and 85**

Claims 84 and 85 depend from claims 1, 36, or 70, and are novel in view of Gao for the same reasons give above regarding claims 1, 36, and 70.

**Tanida I and Tanida II**

Because the Office cited Tanida I in its discussion of Tanida II, these two references are discussed together herein.

Reconsideration is respectfully requested of the rejection of claims 1, 2, 7-10, 14-16, 26, 27, 30-37, 41-45, 49, 50, 60, 61, 64-70, 73, 75-78, 84, and 85 under §102(a) as anticipated by Tanida I, and of the rejection of claims 1, 2, 6-10, 14-16, 26, 27, 30-37, 41-45, 49, 50, 60, 61, 64-70, 73, 75-78, 84, and 85 under §102(b) as anticipated by Tanida II.

The cancellation of claim 6 renders moot its rejection as anticipated by Tanida II; claims 7, 30, 41, 42, and 64 have also been cancelled, rendering moot their rejection as anticipated by Tanida I and Tanida II.

**Claims 1, 2, 8-10, 14-16, 26, 27, and 31-35**

Tanida I and Tanida II describe "capsules for oral preparations, characterized in that, the surface of the capsule base consists of HPMC, a mixture of PEG with HPMC, gelatin, or agar is successively coated with a cationic copolymer and an anionic copolymer" (see col. 2, lines 15-23). Twelve categories of pharmacologically active substances suitable for use with these capsules are disclosed, see col. 3, lines 17-22. Eighty-six specific examples are listed (col. 3, lines 22-52), including celecoxib (col. 3, line 41). In Examples 3-11, Tanida I and Tanida II describe the preparation of capsules

containing prednisolone, calcitonin, 5-fluorouracil, sodium betamethasone phosphate, budesonide, and diclofenac sodium.

Nowhere do Tanida I or Tanida II describe a pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor of the formula shown in claim 1, as amended; a pharmaceutically acceptable glycol or glycol ether; and a turbidity decreasing polymer. None of the compounds in Examples 3-11 have a structure according to the formula shown in claim 1. Thus, claim 1 is novel in view of Tanida I and Tanida II. Similarly, dependent claims 2, 8-10, 14-16, 26, 27, and 31-35 are also novel in view of Tanida I and Tanida II.

Claims 36, 37, 42-45, 49, 50, 60, 61, 65, and 66

As noted hereinabove, and contrary to the Office's suggestion, claim 36 is **not** directed to "an oral formulation comprising a COX-2 inhibitor of low water solubility, a solvent liquid, and a turbidity-decreasing polymer," page 3 of Office Action. Furthermore, claim 36 is novel in view of Tanida I and Tanida II: nowhere do Tanida I or Tanida II describe a pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor of the formula shown in claim 36, as amended; a pharmaceutically acceptable glycol or glycol ether; and a cellulosic polymer. None of the compounds in Examples 3-11 have a structure according to the formula shown in claim 36. Thus, claim 36, and dependent claims 37, 42-45, 49, 50, 60, 61, 65, and 66, are novel in view of Tanida I and Tanida II.

Claims 70, 73, and 75-78

As noted hereinabove, and contrary to the Office's suggestion, claim 70 is **not** directed to "an oral formulation comprising a COX-2 inhibitor of low water solubility, a solvent liquid, and a turbidity-decreasing polymer," page 3 of Office Action. Nevertheless, claim 70 is novel in view of Tanida I and Tanida II: neither Tanida I nor Tanida II describe a specific pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor having the structure shown above in a high energy phase encapsulated within a capsule wall that comprises a turbidity-decreasing polymer, as

claim 70 requires. For the same reasons, dependent claims 73 and 75-78 are also novel in view of Tanida I and Tanida II.

Claims 84 and 85

Claims 84 and 85 depend from claims 1, 36, or 70, and are novel in view of Tanida I and Tanida II for the same reasons give above regarding claims 1, 36, and 70.

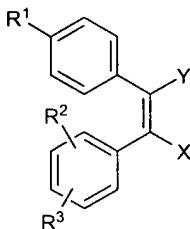
**Black**

Reconsideration is respectfully requested of the rejection of claim 1, 2, 6, 14-16, 21-24, 26, 27, 30, 31, 35-37, 41, 49, 50, 54-57, 60, 61, 64, 65, 69-71, 75-78, and 84-91 under §102(b) as anticipated by Black.

Claims 6, 7, 30, 41, 42, 64, and 71 have been cancelled, thus rendering moot their rejection as being anticipated by Black.

Claims 1, 2, 14-16, 21-24, 26, 27, 31, and 35

Black discloses compounds of Formula I:



wherein X is CH<sub>2</sub>OH, CHO, CO<sub>2</sub>R<sup>4</sup>, or CONR<sup>4</sup><sub>2</sub>; Y is CH<sub>3</sub> or CH<sub>2</sub>OR<sup>5</sup>; and R<sup>1</sup>-R<sup>5</sup> are as defined in the patent, see col. 3, line 30 through col. 4, line 12. These compounds are described as prodrugs of selective COX-2 inhibitors, see col. 6, lines 66-67.

The compounds described Black's Formula I differ from the compound of the formula shown in claim 1: the compound of claim 1 requires a 5- or 6-membered ring substituent (i.e., the ring formed by Y and Z in the structure shown in amended claim 1) substituted by two phenyl rings, while Black's compound requires an ethenylene moiety substituted by two phenyl rings. Nowhere does Black describe a pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor of the formula shown in claim 1, as amended; a pharmaceutically acceptable glycol or glycol ether; and a



turbidity decreasing polymer. Indeed, nowhere does Black describe any pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor of the formula shown in claim 1. Thus, claim 1, and dependent claims 2, 14-16, 21-24, 26, 27, 31, and 35, are novel in view of Black.

Claims 36, 37, 49, 50, 54-57, 60, 61, 65, and 69

Contrary to the Office's suggestion, claim 36 is **not** directed to "an oral formulation comprising a COX-2 inhibitor of low water solubility, a solvent liquid, and a turbidity-decreasing polymer," see page 5 of Office Action.

Claim 36 is novel in view of Black: nowhere does Black describe a pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor of the formula shown in claim 36, as amended; a pharmaceutically acceptable glycol or glycol ether; and a cellulosic polymer. None of the compounds in Examples 3-11 have a structure according to the formula shown in claim 36. Thus, claim 36, and dependent claims 37, 42-45, 49, 50, 60, 61, 65, and 66, are novel in view of Tanida I and Tanida II.

Claims 70 and 75-78

As noted hereinabove, and contrary to the Office's suggestion, claim 70 is **not** directed to "an oral formulation comprising a COX-2 inhibitor of low water solubility, a solvent liquid, and a turbidity-decreasing polymer," see page 5 of Office Action.

Claim 70 is novel in view of Black: Black does not describe a specific pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor having the structure shown above in a high energy phase encapsulated within a capsule wall that comprises a turbidity-decreasing polymer, as claim 70 requires. For the same reasons, dependent claims 73 and 75-78 are also novel in view of Black.

Claims 84-91

Claims 84-91 depend from claims 1, 36, or 70, and are novel in view of Black for the same reasons give above regarding claims 1, 36, and 70.

***CLAIM REJECTIONS UNDER 35 U.S.C. §103***

**Gao in view of Hanna**

Reconsideration is respectfully requested of the rejection of claims 4, 5, 17-19, 24, 25, 39, 42, 51-53, 58, 59, and 79-81 under §103(a) as unpatentable over Gao in view of Hanna.

**Claims 4, 5, 17-19, 24, and 25**

Claim 4 is directed to the composition of claim 1 wherein at least about 15% of the drug is present in the solvent liquid in dissolved or solubilized form. Claim 5 is directed to the composition of claim 1 wherein substantially all of the drug is present in the solvent liquid in dissolved or solubilized form.

Claim 17 is directed to the composition of claim 1 wherein the turbidity-decreasing polymer is HPMC, and wherein the HPMC has about 15% to about 35% methoxyl substitution and about 3% to about 15% hydroxypropoxyl substitution. Claim 18 is directed to the composition of claim 1 wherein the turbidity-decreasing polymer is HPMC, and wherein the HPMC has about 19% to about 30% methoxyl substitution and about 4% to about 12% hydroxypropoxyl substitution; and claim 19 is directed to the composition of claim 1 wherein the turbidity-decreasing polymer is HPMC, and wherein the HPMC has about 19% to about 24% methoxyl substitution and about 7% to about 12% hydroxypropoxyl substitution.

Claim 24 is directed to the composition of claim 1 wherein the turbidity-decreasing polymer is present in the solvent liquid in an amount of about 1% to about 20% by weight of the solvent liquid, and claim 25 is directed to the composition of claim 1 wherein the turbidity-decreasing polymer is present in the solvent liquid in an amount of about 1% to about 15% by weight of the solvent liquid.

Hanna describes controlled release dosage forms comprising acetaminophen, pseudoephedrine or a pharmaceutically acceptable salt thereof, dextbrompheniramine or a pharmaceutically acceptable salt thereof, a polymer, and excipients. The preferred

polymer is HPMC. In addition, Hanna states that one or more fillers are also present in these compositions; suitable fillers are lactose and dibasic calcium phosphate dihydrate (the preferred filler). Hanna also states that the compositions contain one or more lubricating agents, e.g., stearic acid, magnesium stearate, calcium stearate, waxes, PEG, or magnesium lauryl sulfate; a preferred embodiment comprises 0.9-1.7% stearic acid and 0.25-0.78 magnesium stearate.

The Office has not established a *prima facie* case of obviousness with respect to claims 4 and 5. Specifically, the Office has not shown that there is any suggestion or motivation to modify the cited references to arrive at the claimed compositions. The Office has not because it cannot.

As noted above, Gao describes pharmaceutical compositions comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg. These pharmaceutical compositions may also comprise one or more carrier materials or excipients selected from diluents, disintegrants, binding agents, wetting agents, and lubricants. Nowhere does Gao describe the specific combination of a selective cyclooxygenase-2 inhibitor of the formula shown in claim 1, a pharmaceutically acceptable glycol or glycol ether, and a turbidity decreasing polymer, nor does Gao describe such a combination wherein at least about 15% of the drug is present in the solvent liquid in dissolved or solubilized form (as required by claim 4) or wherein substantially all of the drug is present in the solvent liquid in dissolved or solubilized form (as required by claim 5).

As noted above, Gao states that her pharmaceutical compositions may also comprise one or more carrier materials or excipients selected from diluents, disintegrants, binding agents, wetting agents, and lubricants. These carrier materials or excipients are discussed in the specification as shown below:

Diluents	page 20, lines 6-27	At least twenty-six suitable diluents are named; lactose and microcrystalline cellulose, either individually or in combination, are preferred diluents, and lactose (especially lactose monohydrate) is particularly preferred.
Disintegrants	page 21, lines 1-9	Eight different classes of disintegrants suitable for use in the compositions are described; croscarmellose sodium is named as a preferred disintegrant for tablet or capsule disintegration.
Binding agents	page 21, line 20 through page 22, line 7	At least twenty binding agents or adhesives are listed, including cellulose materials such as, but not limited to, methylcellulose and sodium carboxymethylcellulose (e.g., Tylose), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (Klucel), and ethylcellulose (Ethocel); polyvinylpyrrolidone is a preferred binding agent used to impart cohesive properties to a powder blend of celecoxib and other excipients for granulation of a celecoxib formulation.
Wetting agents	page 22, lines 17-31	At least nine wetting agents, including the preferred wetting agent (sodium lauryl sulfate), are listed.
Lubricants	page 23, lines 3-15	At least seventeen lubricants, including PEGs such as Carbowax 4000 and Carbowax 6000, are listed; magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

As the Office indicated, the instant specification names polyvinylpyrrolidone and cellulosic polymers such as HPMC as examples of suitable turbidity-decreasing

polymers (see page 27, lines 8-23 and Example 1); claims 4 and 5 are not limited to any particular turbidity-decreasing polymer. PEG is named as a suitable solvent (see page 24, lines 25-26), but claims 4 and 5 are not limited to any particular glycol or glycol ether. Gao named HPMC and polyvinylpyrrolidone as two of twenty suitable binding agents; polyvinylpyrrolidone was named as a preferred binding agent used to impart cohesive properties to a powder blend of celecoxib and other excipients for granulation of a celecoxib formulation. Gao included PEG in a list of seventeen suitable lubricants, but nowhere does Gao suggest that PEG is a preferred lubricant.

Nothing in Gao would have motivated one skilled in the art to prepare the composition of claims 4 or 5. While Gao mentions the use of binding agents and/or lubricants in her compositions, nowhere does she describe a composition having, for example, (a) HPMC as the binding agent and PEG as the lubricant, (b) polyvinylpyrrolidone as the binding agent and PEG as the lubricant, or (c) any turbidity-decreasing polymer and any glycol or glycol ether. Indeed, in the only examples that describe a composition comprising a glycol (i.e., Example 11-1 and 11-2, formulation E), the only other excipient included in the composition is water. ("The vehicle for the intravenous and oral solution doses was a mixture of polyethylene glycol having an average molecular weight of 400 (PEG-400) and water in a ratio of 2:1 by volume." See page 45, lines 16-18.)

Hanna fails to supply the motivation to combine that Gao lacks. Nowhere does Hanna describe a composition according to claims 4, 5, 17-19, 24, or 25, or suggest its preparation. Indeed, nowhere does Hanna describe any compound of the formula shown above, nor does Hanna describe a composition wherein such a drug is present in a solvent liquid consisting of glycols and glycol ethers in dissolved or solubilized form. In Hanna's Example 1, the only glycol is present in the tablet coating, and there is no suggestion or description that any portion of the drugs Hanna does disclose are dissolved in the glycol.

The Office asserts that the requirement of claims 4 or 5 that specify that a certain amount of the drug is present in the solvent liquid in dissolved or solubilized form "hold[s] little patentable weight [in] view of the prior art," and that "[t]he prior art discloses a composition where the components are dissolved in a solvent liquid," see page 7, lines 8-9. However, as noted above, claims 4 and 5 do not merely require that the drug be in dissolved or solubilized form in the solvent liquid; these claims depend from claim 1, and therefore include all the limitations of that claim, for example, that the composition comprises a turbidity-decreasing polymer. Nowhere do Gao or Hanna describe such a composition or suggest its preparation.

In addition, the Office asserts that:

Gao discloses a celecoxib formulation comprising hydroxypropylmethylcellulose. What is lacking in the reference is a disclosure of the particular methoxyl and hydroxypropoxyl substitution concentration. Hanna et al discloses a formulation comprising a hydroxypropyl-methylcellulose with about 19% to about 24% methoxyl substitution and about 7% to about 12% hydroxypropoxyl substitution. . . . It would have been obvious to one of ordinary skill in the art to combine the hydroxypropyl-methylcellulose of Hanna with the formulation of Gao.

Office Action, paragraph bridging pages 6 and 7. However, regardless of whether Hanna describes HPMC having the methoxyl and hydroxypropoxyl substitution described above, claims 4 and 5 do not require such substitution. Furthermore, as noted above, Gao already describes compositions comprising celecoxib and HPMC; the portion of Hanna cited by the Office adds nothing to Gao.

The Office has not shown that one skilled in the art would have been motivated to combine Gao and Hanna and to modify these references to arrive at the compositions of claims 4 and 5. Thus, the Office has not established a *prima facie* case of obviousness with respect to claims 4 and 5.

Similarly, the Office has not established a *prima facie* case of obviousness with respect to claims 17-19. Specifically, the Office has not shown that one skilled in the art

would have been motivated to combine Gao and Hanna and to modify these references to arrive at the compositions of claims 17-19. The Office asserts that it would have been obvious to one of ordinary skill in the art to combine the hydroxypropyl-methylcellulose of Hanna with the formulation of Gao. Applicants respectfully disagree. There is nothing in Gao that would have motivated one skilled in the art to select HPMC from the numerous binding agents Gao describes; indeed, while Gao lists HPMC as a possible binding agent, Gao names polyvinylpyrrolidone as a preferred binding agent used to impart cohesive properties to a powder blend of celecoxib and other excipients for granulation of a celecoxib formulation. Nothing in Gao or Hanna would have led one skilled in the art to consider selecting HPMC from all the binding agents disclosed, and to combine HPMC with celecoxib and a solvent selected from glycols and glycol ethers.

Likewise, the Office has not established a *prima facie* case of obviousness with respect to claims 24 and 25. Specifically, the Office has not shown that one skilled in the art would have been motivated to combine Gao and Hanna and to modify these references to arrive at the compositions of claims 24 and 25, for the same reasons given above with respect to claims 4 and 5.

Claims 39, 51-53, 58, and 59

Claim 39 is directed to the composition of claim 36 wherein at least about 15% of the drug is present in the solvent liquid in dissolved or solubilized form.

Claim 51 is directed to the composition of claim 36 wherein the cellulosic polymer is HPMC and wherein the HPMC has about 15% to about 35% methoxyl substitution and about 3% to about 15% hydroxypropoxyl substitution; claim 52 is directed to the composition of claim 36 wherein the cellulosic polymer is HPMC and wherein the HPMC has about 19% to about 30% methoxyl substitution and about 4% to about 12% hydroxypropoxyl substitution; and claim 53 is directed to the composition of claim 36 wherein the cellulosic polymer is HPMC and wherein the HPMC has about 19% to about 24% methoxyl substitution and about 7% to about 12% hydroxypropoxyl substitution.

Claim 58 is directed to the composition of claim 36 wherein the cellulosic polymer is present in the solvent liquid in an amount of about 1% to about 20% by weight of the solvent liquid, and claim 59 is directed to the composition of claim 36 wherein the cellulosic polymer is present in the solvent liquid in an amount of about 1% to about 15% by weight of the solvent liquid.

The Office has not established a *prima facie* case of obviousness with respect to claim 39. Specifically, the Office has not shown that there is any suggestion or motivation to modify the cited references to arrive at the claimed compositions. The Office has not because it cannot.

Nowhere does Gao describe the specific combination of a selective cyclooxygenase-2 inhibitor of the formula shown in claim 36, a pharmaceutically acceptable glycol or glycol ether, and a cellulosic polymer, nor does Gao describe such a combination wherein at least about 15% of the drug is present in the solvent liquid in dissolved or solubilized form (as required by claim 39).

As noted above, Gao states that her pharmaceutical compositions may also comprise one or more carrier materials or excipients selected from diluents, disintegrants, binding agents, wetting agents, and lubricants. These carrier materials or excipients are discussed in the specification as shown above.

As the Office indicated, the instant specification names HPMC as an example of a suitable cellulosic polymers, but claim 39 is not limited to any particular cellulosic polymer. PEG is named as a suitable solvent (see page 24, lines 25-26), but claim 39 is not limited to any particular glycol or glycol ether. Gao named HPMC as one of twenty suitable binding agents; polyvinylpyrrolidone was named as a preferred binding agent used to impart cohesive properties to a powder blend of celecoxib and other excipients for granulation of a celecoxib formulation. Gao included PEG in a list of seventeen suitable lubricants, but nowhere does Gao suggest that PEG, or any other glycol or glycol ether, is a preferred lubricant.



Nothing in Gao would have motivated one skilled in the art to prepare the composition of claim 39. While Gao mentions the use of binding agents and/or lubricants in her compositions, nowhere does she describe a composition having HPMC or any other cellulosic polymer as the binding agent and PEG or any other glycol or a glycol ether as the lubricant. Indeed, in the only examples that describe a composition comprising a glycol, the only other excipient included in the composition is water.

Hanna fails to supply the motivation to combine that Gao lacks. Nowhere does Hanna describe a composition according to claim 39, or suggest its preparation. Indeed, nowhere does Hanna describe any compound of the formula shown above, nor does Hanna describe a composition wherein such a drug is present in a solvent liquid consisting of glycols and glycol ethers **in dissolved or solubilized form**. In Hanna's Example 1, the only glycol is present in the tablet coating, and there is no suggestion or description that any portion of the drugs Hanna does disclose are dissolved in the glycol.

The Office asserts that the requirement of claim 39 that specifies that a certain amount of the drug is present in the solvent liquid in dissolved or solubilized form "hold[s] little patentable weight [in] view of the prior art," and that "[t]he prior art discloses a composition where the components are dissolved in a solvent liquid," see page 7, lines 8-9. However, as noted above, claim 39 does not merely require that the drug be in dissolved or solubilized form in the solvent liquid; this claim depends from claim 36, and therefore includes all the limitations of that claim, for example, that the composition comprises a cellulosic polymer. Nowhere do Gao or Hanna describe such a composition or suggest its preparation.

The Office has not shown that one skilled in the art would have been motivated to combine Gao and Hanna and to modify these references to arrive at the compositions of claim 39. Thus, the Office has not established a *prima facie* case of obviousness with respect to claim 39.

Similarly, the Office has not established a *prima facie* case of obviousness with respect to claims 51-53. Specifically, the Office has not shown that one skilled in the art would have been motivated to combine Gao and Hanna and to modify these references to arrive at the compositions of claims 51-53. The Office asserts that it would have been obvious to one of ordinary skill in the art to combine the hydroxypropylmethylcellulose of Hanna with the formulation of Gao. Applicants respectfully disagree. There is nothing in Gao that would have motivated one skilled in the art to select HPMC from the numerous binding agents Gao describes; indeed, while Gao lists HPMC as a possible binding agent, Gao names polyvinylpyrrolidone as a preferred binding agent used to impart cohesive properties to a powder blend of celecoxib and other excipients for granulation of a celecoxib formulation. Nothing in Gao or Hanna would have led one skilled in the art to consider selecting HPMC from all the binding agents disclosed, and to combine HPMC with celecoxib and a solvent selected from glycols and glycol ethers.

Likewise, the Office has not established a *prima facie* case of obviousness with respect to claims 58 and 59. Specifically, the Office has not shown that one skilled in the art would have been motivated to combine Gao and Hanna and to modify these references to arrive at the compositions of claims 58 and 59, for the same reasons given above with respect to claim 39.

#### Claims 79-81

Claim 79 is directed to the composition of claim 70 wherein the turbidity-decreasing polymer is HPMC and wherein the HPMC has about 15% to about 35% methoxyl substitution and about 3% to about 15% hydroxypropoxyl substitution; claim 80 is directed to the composition of claim 70 wherein the turbidity-decreasing polymer is HPMC and wherein the HPMC has about 19% to about 30% methoxyl substitution and about 4% to about 12% hydroxypropoxyl substitution; and claim 81 is directed to the composition of claim 70 wherein the turbidity-decreasing polymer is HPMC and wherein the HPMC has about 19% to about 24% methoxyl substitution and about 7% to about 12% hydroxypropoxyl substitution.

The Office has not established a *prima facie* case of obviousness with respect to claims 79-81. Specifically, the Office has not shown that the cited references recite every element of these claims. Nowhere do Gao or Hanna describe a specific pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor having the structure shown above in a high energy phase **encapsulated within a capsule wall that comprises a turbidity-decreasing polymer**, as claims 79-81 requires.

Furthermore, the Office has not shown that one skilled in the art would have been motivated to combine Gao and Hanna and to modify these references to arrive at the compositions of claims 79-81.

#### **Tanida II or Gao in view of Guess**

Reconsideration is respectfully requested of the rejection of claims 13 and 48 under §103(a) as unpatentable over Tanida II or Gao in view of Guess.

Claim 13 is directed to the composition of claim 1 wherein the drug is valdecoxib, and claim 48 is directed to the composition of claim 36 wherein the drug is valdecoxib.

The Office has not established a *prima facie* case of obviousness with respect to claims 13 and 48. Specifically, the Office has not shown that one skilled in the art would have been motivated to combine either of Tanida II or Gao with Guess and to modify these references to arrive at the compositions of claim 13 or 48.

Neither Tanida II nor Gao, taken alone or in combination with Guess, describe or even suggest the compositions of claims 13 and 48. Tanida II and Gao are discussed in detail above. Guess describes tachykinin receptor antagonists, e.g., a neurokinin-1 receptor antagonist, useful for treatment or prevention of nonbacterial prostatitis and/or prostatodynia. Guess mentions that the tachykinin receptor antagonist may be administered in combination with another drug, including a selective COX-2 inhibitor (see col. 32, lines 48-54). Several selective COX-2 inhibitors are named, including celecoxib and valdecoxib (see col. 33, lines 18-19).

The Office has not demonstrated that one skilled in the art would have been motivated to combine the celecoxib-PEG solution disclosed in Gao (see Examples 11-1

and 11-2) with the capsules described by Tanida II, and then to replace the celecoxib in Gao with the valdecoxib mentioned by Guess. Tanida II mentions celecoxib as one of 86 drugs that may be formulated in the capsules described. Tanida mentions that COX-2 inhibitors are the preferred anti-inflammatory agent, but does not indicate that anti-inflammatory agents are particularly suited for use with the capsules described; nor does Tanida II suggest a preference for selecting celecoxib rather than any of the other drugs recited.

### **Tanida II**

Reconsideration is respectfully requested of the rejection of claims 28, 29, 62, 63, 82, and 83 under §103(a) as unpatentable over Tanida II. The Office has not established a *prima facie* case of obviousness with respect to claims 28, 29, 62, 63, 82, and 83: nowhere does Tanida II describe a specific pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor encapsulated within a capsule wall that comprises a turbidity-decreasing polymer (as required by claims 28, 29, 82, and 83) or a cellulosic polymer (as required by claims 62 and 63).

### **Tanida II in view of Kawata**

Reconsideration is respectfully requested of the rejection of claim 74 under §103(a) as unpatentable over Tanida II in view of Kawata. The Office has not established a *prima facie* case of obviousness with respect to claim 70: neither Tanida II (as noted above) nor Kawata describe a specific pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitor encapsulated within a capsule wall that comprises a turbidity-decreasing polymer.

3407/1/US

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### **CONCLUSION**

Applicants submit that the present invention is now in condition for allowance.  
Early allowance of all pending claims is respectfully solicited.

Respectfully submitted,



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Enclosures:

Transmittal Letter  
Combined Amendment Transmittal and  
Request for Extension of Time  
Fee Transmittal  
Itemized Postcard